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APR 77 L KAUFMAN, S J WILLIAMSON

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Instrumentation and procedures for detecting neuromagnetic fields evoked by sensory stimuli in an unshielded environment are described. Latencies of somatosensory and visually evoked neuromagnetic responses are compared with simple reaction times. Assuming a serial model, the RT can be divided into motor and sensory components. The latter is reflected in the neuromagnetic response. The visual neuromagnetic response has revealed two functionally distinct components that may reflect activity of sustained channels. It has also permitted isolation of two

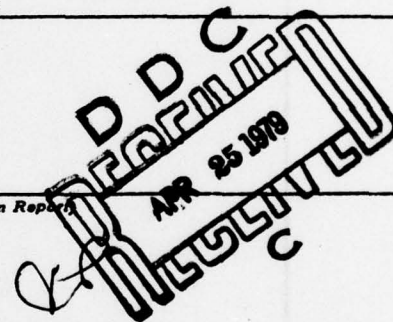
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20. ↓ distinct cortical regions with different response properties. Latencies of response of each of the two hemispheres were studied and revealed marked individual differences. ↗

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THE EVOKED MAGNETIC FIELD OF THE HUMAN BRAIN¹

By Lloyd Kaufman and Samuel J. Williamson

The electrical activity of the human brain has long been of interest to physiologists and psychologists. Electrical recordings from single cells in the brains of animals are highly suggestive of processes underlying human perception. However, for ethical reasons study of the normal human brain is largely restricted to measuring changes in potential differences between electrodes applied to the scalp. These differences are produced by the flow of weak electrical currents in the dermis and occur because the brain is a volume conductor. Current flowing between two points within the brain as a result of biological activity produces within the volume conductor an accompanying current which spreads through the skull and outward to the dermis. Consequently, active neural tissue produces effects that may be detected at great distances. This leads to some blurring of the effects produced by different active regions of the brain, since even widely separated sources produce superimposed effects at the detecting electrodes. Despite the obvious limitations resulting from this state of affairs, many important insights have been gained by sophisticated researchers from measurements of potential differences at the scalp (Desmedt, 1977).

A major advantage could accrue from using a detecting system that is insensitive to the weak currents in the skin but is sensitive to the primary higher density current at the source in the brain. Such a method could provide finer spatial resolution and may therefore furnish information about functionally distinct populations of neurons. We will describe such a method and some of the results obtained by its use. This method employs a superconducting device sensitive to extremely weak magnetic fields outside the scalp produced by the flow of current within the brain itself. Moreover, this new method has been developed to the point where it may be employed in a normal unshielded

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laboratory environment. It is now established that fields produced by functionally and anatomically separate portions of the brain may be discriminated by this method.

Some readers may be unfamiliar with the physical principles underlying the new method. Others may not be familiar with the physiological and psychological considerations basic to the experiments that employ this new method. Therefore, our approach will be largely didactic in nature.

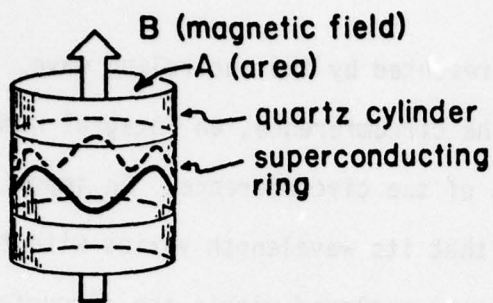
Superconductivity and Detecting Weak Magnetic Fields

On July 10, 1908, after many years of work, the Dutch physicist Kammerlingh Onnes succeeded in liquifying helium. Its boiling point was found to be at about 4° K. Onnes ultimately reduced the temperature of his liquid helium to 1.4° K and set out to study the behavior of matter at such very low temperatures. It was already known that the electrical resistance of metals falls with temperature. Onnes found this effect to be greater in pure metals than in those containing impurities. A sample of pure mercury displayed a surprising kind of behavior. As its temperature was lowered, at about 3° K the mercury abruptly lost all resistance. This discovery in 1911 led to the finding that lead, tin and many other metals also lose all resistance to electricity at particular "critical" temperatures. In 1913 Onnes first used the term superconductivity to describe this phenomenon.

Nearly fifty years were to elapse before an explanation for this and several other puzzling effects appeared. In 1957 Bardeen, Cooper and Schrieffer introduced a theory showing that at sufficiently low temperatures electrons become associated in pairs and that the behavior of each pair can then be described in quantum theory by the same wave function.

The upper panel in Figure 1 illustrates a relevant example. The superconductor is a closed ring, perhaps formed by depositing a film of lead or niobium onto a cylindrical quartz form. The wave function describing the

Insert Figure 1 about here



quantum theory gives

$$\text{flux} = B \times A$$

$$= \phi_0, 2\phi_0, 3\phi_0, \dots$$

where the quantity ϕ_0 is called the "flux quantum".

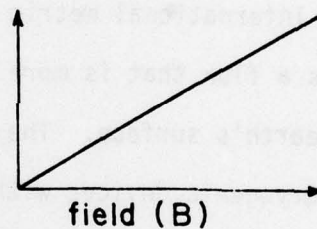
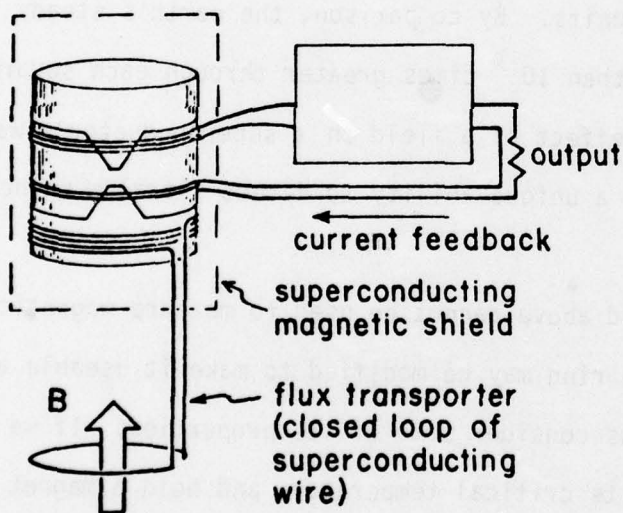
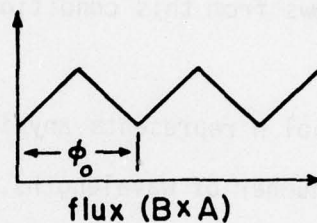
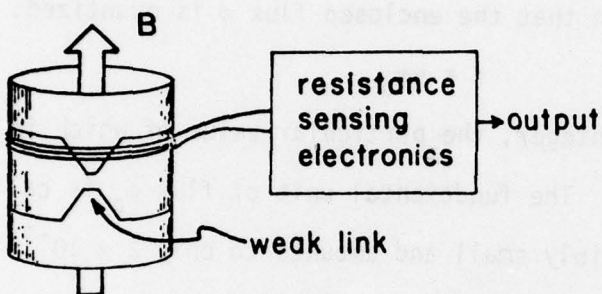


Figure 1. Principles on which the SQUID magnetic field detection system is based. The upper panel illustrates the quantization of magnetic flux within any area bounded by a superconductor. The center panel shows how a properly designed weak link in the superconductor allows one flux quantum at a time to enter the area when a magnetic field is imposed on the SQUID. The bottom panel indicates how a negative feedback current can be arranged to set up an appropriate field to maintain the total flux within the SQUID invariant.

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superconducting electron state is represented by the encircling wave. For it to join smoothly onto itself around the circumference, an integral number of wavelengths must add up to the length of the circumference. An important feature of the superconducting state is that its wavelength varies with the total magnetic flux (product of field and area) enclosed within the circumference. It follows from this condition that the enclosed flux ϕ is quantized:

$$\phi = n\phi_0.$$

The symbol n represents any integer, the particular value of which is related to the number of wavelengths. The fundamental unit of flux ϕ_0 is called the "flux quantum". It is incredibly small and amounts to only 2×10^{-15} tesla-square meter. The "tesla" is a measure of magnetic field strength in the Système International metric units. By comparison, the earth's steady field produces a flux that is more than 10^{10} times greater through each square meter of the earth's surface. The effect of a field on a superconductor's wavelength endows cryogenic devices with a unique ability to detect ultralow magnetic fields.

The simple ring described above cannot be used to measure magnetic fields. Before considering how such a ring may be modified to make it useable as a detector of magnetic fields, let us consider some of its properties. If we cool the ring to a temperature below its critical temperature and hold a magnet near it while doing so, the flux initially within the ring remains trapped there even after the magnet is removed! This quantized flux is maintained by an electric current flowing on the inside surface of the ring. This current can flow indefinitely because there is no electrical resistance in a superconductor. Also, if the magnet is brought close again, a similar shielding current will flow on the outside surface of the ring to keep the magnet's field from penetrating the material. This property of the ring which keeps fields from entering is an example of the "Meissner effect". In brief, what's inside is kept in and what's

outside is kept out.

A simple alteration of the ring converts it into a useful device. As illustrated in the center panel of Figure 1, the ring may be cut away at one place to leave only a narrow bridge or "weak link". Then it is possible to force non-integral multiples of ϕ_0 through the weak link into the interior of the ring. However, the link then has a higher energy and cannot support an indefinitely large current. The increase in energy is called the "Josephson coupling energy", and the weak link behaves as a "Josephson junction." In 1962 Josephson predicted this remarkable effect for an analogous situation of two superconductors separated by a thin insulating barrier. If the geometry of the weak link is appropriately designed, the increase in energy makes the superconducting state unstable when it shields the equivalent of about one flux quantum. The weak link will then suddenly convert to the normal metallic state and allow the amount of one flux quantum to enter. Thereupon, with less demand for shielding, the link reverts to the superconducting state. This process will be repeated periodically if the applied magnetic field is caused to steadily increase.

By introducing a suitable radio frequency circuit, the condition of the ring can be monitored and the periodic response recorded, as illustrated in the center panel of Figure 1 (Zimmerman, et al., 1970). The cryogenic element is known colloquially as a SQUID (for superconducting quantum interference device). Several other types of SQUIDs have been used successfully for low field measurements (Clarke, 1974).

The periodic response of the system just described permits measurements of magnetic field in units of the flux quantum. However, an improvement by a factor of more than 10^4 in sensitivity can be gained by a simple innovation (Zimmerman, et al., 1970). Suppose that the electronic circuit monitoring the SQUID also provides a feedback current that flows through a coil wrapped around the

SQUID. If the feedback current has the proper value to cancel the effect of any applied field, a change in this feedback current will be proportional to changes in the applied field. Such changes can be indicated by the voltage developed across a resistor through which the current passes, as shown in the bottom panel of Figure 1. This arrangement provides a desired voltage output that increases linearly with field, as illustrated. Without going into the details of how the feedback signal is generated, it is sufficient here to point out that the system responds to fields whose temporal variation may range from dc to some high frequency. The upper frequency limit is determined by the characteristics of the electronics associated with the SQUID. These devices do not depend on ordinary Faraday induction as indicated by the fact that they respond to the field per se and not to its time derivatives. Such SQUIDs have become a common measuring instrument in the laboratories of low temperature physicists.

For many purposes a major advantage is gained if the SQUID itself is not employed to sense the magnetic field but instead is shielded within a superconducting chamber. This chamber excludes all magnetic fields but that which is supplied by a superconducting circuit known as a flux transporter. A simple flux transporter is depicted in the bottom panel of Figure 1. It is a closed circuit formed from a piece of superconducting wire. The circuit includes a primary coil ("detection coil") and another "input coil" which is contained in the superconducting chamber with the SQUID. There is a close magnetic coupling between the input coil and the SQUID. Consequently, whenever a magnetic field is imposed on the detection coil, which may be a long distance from the SQUID, the responding electric current flows around the circuit so that the total magnetic flux within the transporter remains invariant, as it did with the superconducting ring described above. The current flowing through the secondary (input) coil establishes a magnetic field which is sensed by the SQUID.

The electronic monitor of the SQUID thereby provides a voltage that is strictly proportional to the net magnetic flux imposed on the detection coil.

A simple flux transporter combined with a SQUID as illustrated in the bottom panel of Figure 1 is known as a magnetometer. It responds to any magnetic field imposed on the detection coil -- even steady fields. When employing such a device to measure weak fields produced by a source in the vicinity of the detection coil the effect of the field of interest may be masked by stronger fields in the environment. Thus, the earth's steady field will also be sensed by the magnetometer as would fields produced by electrical machinery. One approach to eliminating these effects of unwanted signals is to enclose the SQUID and its associated circuitry together with the object being studied in a magnetically shielded room. In a properly designed magnetically shielded room ultralow fields may be measured without disturbance by extraneous fields. As we shall see later, it is now possible to employ a specially designed flux transporter that makes it possible to employ the SQUID in a normal laboratory environment.

SQUID detection systems are immersed in liquid helium which is contained within a fiberglass, vacuum insulated container known as a dewar. A typical dewar, the one employed in our laboratory, is illustrated in Figure 2.

Insert Figure 2 about here

Biomagnetism

In the 19th century the French scientists Biot and Savart enunciated a law that bears their names. According to the Biot-Savart law, the movement of an electric charge produces a magnetic field in the surrounding space. Since currents flow within the human body, they must accordingly be accompanied by magnetic fields. We coined the term biomagnetism to stand for the study of magnetic fields arising within an organism (Williamson, Kaufman, and Brenner, 1977). Many of these fields are so weak that superconducting devices are

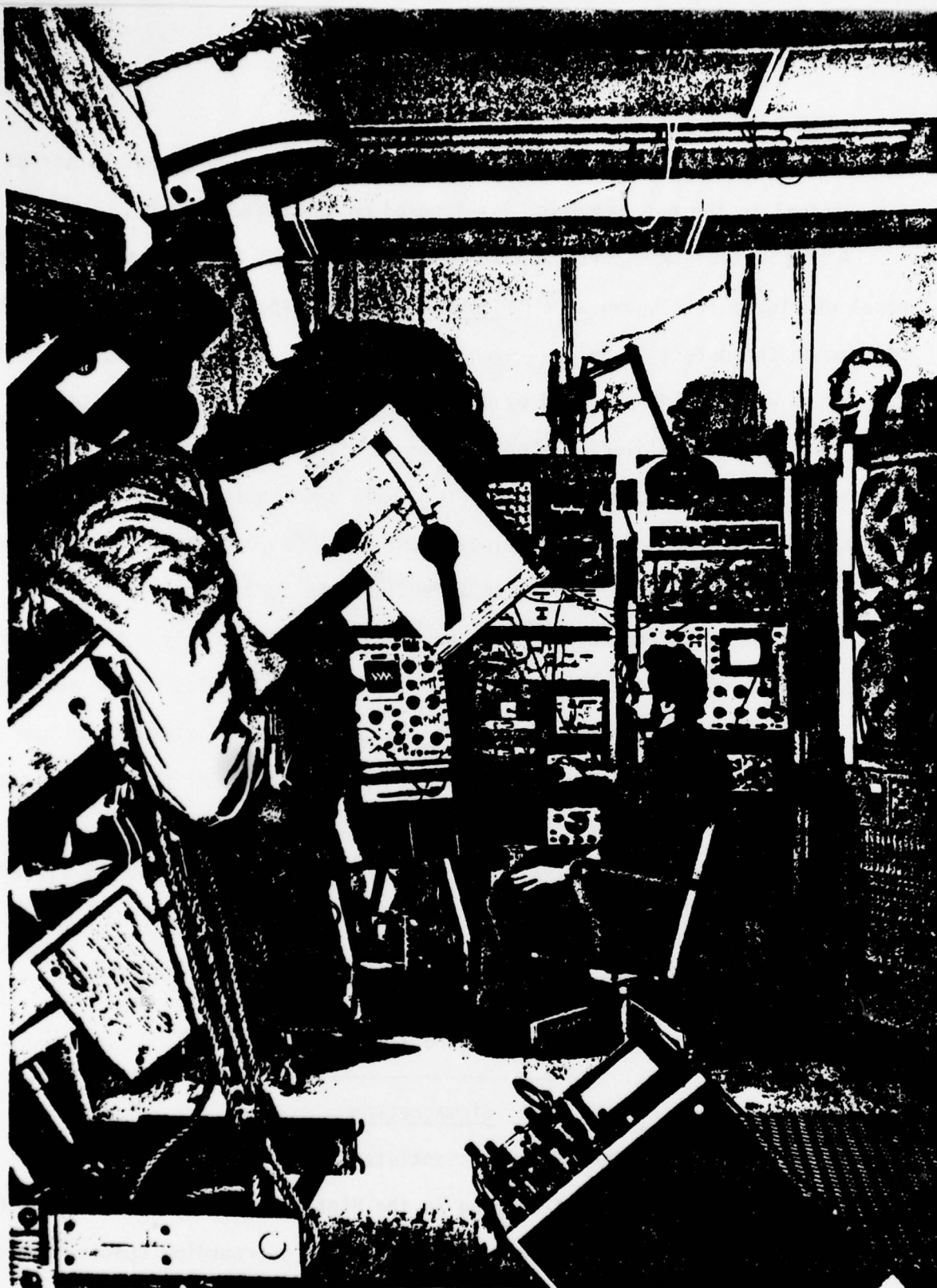


Figure 2. Arrangement of subject, oscilloscope presenting the visual display, dewar, and signal averaging electronics in the Neuromagnetism Laboratory of New York University. The protruding tail of the dewar containing the detection coil of the flux transporter is positioned near the visual cortex at the back of the head.

needed to detect them. This is not true for all such magnetic fields. For example, in 1963 Baule and McFee first detected the QRS peak of the magneto-cardiogram with induction coils. This result was confirmed by Cohen (1967) and by Safonov and his colleagues (1967). Subsequently, by cross-correlating the conventional EEG with the output of an induction coil placed near the scalp, Cohen (1968) was able to detect components of the magnetoencephalogram at alpha frequencies. This procedure does not allow the detection of magnetic fields that are uncorrelated with the ordinary electroencephalogram. Nevertheless, it provided evidence for the fact that there are detectable magnetic fields associated with the flow of current in the human brain.

The SQUID was first applied in biomagnetism during a study of the magneto-cardiogram (Cohen, Edelsack and Zimmerman, 1970). This cryogenic detector made it possible to measure biomagnetic phenomena that differ in important ways from those that are detectable with conventional electrodes. For example, steady fields associated with dc phenomena having no counterparts in conventional measures of potential differences were detected for the first time. Several reviews of biomagnetic studies are now available (Cohen, et al., 1976; Williamson, Kaufman, and Brenner, 1977; Reite and Zimmerman, 1978). Before turning to our own work - which is the major concern of this article - it is worth mentioning some of the other discoveries in the new field of biomagnetism. One particularly noteworthy finding is the difference between the fetal electrocardiogram and the fetal magnetocardiogram discovered in Finland (Karinemi, et al., 1974). Both phenomena are depicted in Figure 3. The fetal electrocardiogram was detected

Insert Figure 3 about here

by placing one electrode on the mother's abdomen and the other elsewhere on her body but far from her heart. Even so, it is obvious that the predominant signal is the mother's heart beat which masks the heartbeat of the fetus. This is due

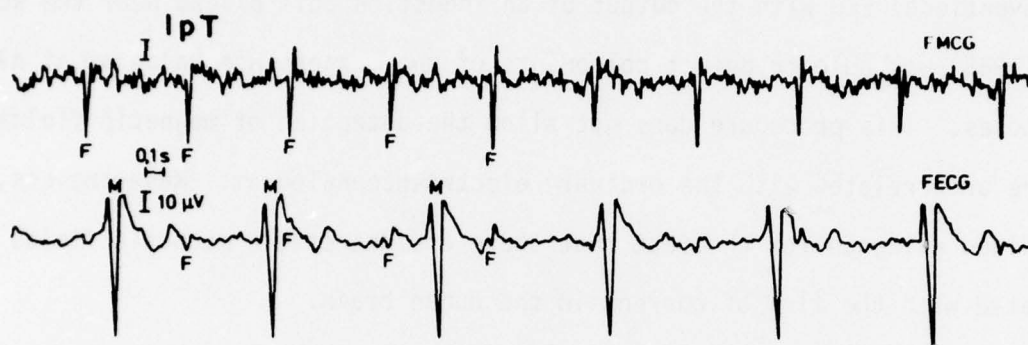


Figure 3. Fetal magnetocardiogram and electrocardiogram after 29 weeks' gestation recorded by V. Kariniemi et al. of the Department of Technical Physics at the Helsinki University of Technology and the First Department of Obstetrics and Gynecology at the Helsinki University Central Hospital. This is particularly graphic example of the better resolution of the fetal heart signal (f) relative to the mother's signal (M) afforded by magnetic detection.

to the fact that the body is a volume conductor and weak currents are therefore present in the dermis. The fetal magnetocardiogram was detected simply by placing the detection coil of a SQUID detector over the mother's abdomen. This detection coil responded to the strongest nearby source which, in this case, is the fetus' heart. Skin currents produced by the mother's heart were of low density and therefore too weak to be detected by the magnetometer.

A group in Grenoble studied a large population of patients with various types of heart disease (Matelin, 1974). Patients were also studied at Stanford and their vector electrocardiograms were compared with their vector magnetocardiograms (Barry, et al., 1978). These data suggest that the normal vector electro- and magnetocardiograms are highly correlated but this correlation may break down when the heart is abnormal. This subject warrants further study with larger populations, and such work is now underway in several countries.

In addition to work on the heart and brain there is considerable interest in measuring the amount of magnetic contaminants in the lung, e.g., as in the case of arc welders or miners. This topic lies outside the scope of this paper as is the study of the presence of iron in the liver or heart muscle as a result of various disease processes.

Hughes and his colleagues (1976), working in a magnetically shielded room, studied the spontaneous magnetoencephalogram (MEG) and compared it with the conventional EEG. The two measures are only partially correlated. When alpha rhythms were absent in the EEG it was not possible to predict the spectral composition of the MEG. However, alpha rhythms in the EEG enable one to predict their presence in the MEG. But even here the correlation is not perfect since one cannot predict the phase of one signal from the other.

Also working in a magnetically shielded room, Teyler, Cuffin, and Cohen (1975) detected changes in the magnetic field of the brain in response to a flashed strobe light. At about the same time in collaboration with D. Brenner we succeeded

in detecting the response of the brain to a periodically flashed visual pattern without employing shielding (Brenner, Williamson, and Kaufman, 1975).

Bringing the SQUID into the Laboratory

As already indicated, the SQUID magnetometer has been used in a magnetically shielded room to isolate it from extraneous magnetic signals. However, it is difficult to conduct certain experiments even when a shielding environment is available. This is particularly true in studies of the response of the brain to visual stimulation. The mere introduction of electronic equipment to produce visual displays can defeat the purpose of the shielding. Fortunately, an alternative strategy is available to make it possible to employ the SQUID in a normal, unshielded laboratory environment. The principle underlying this strategy is quite simple. It works because most background fields are relatively uniform in space since their sources are far away. By contrast, fields from the human body diminish rapidly with distance from the skin. The geometry of the detection coil can be chosen to render it insensitive to relatively uniform fields while retaining sensitivity to those from nearby sources. Figure 4 illustrates the possibilities. The left-hand example (A) provides no advantage because the detection

Insert Figure 4 about here

coil or magnetometer responds to any field linking the coil. But the configuration B with two loops wound in opposite directions discriminates against any uniform field: a positive magnetic flux linking one loop is cancelled by a negative flux in the other. Yet this gradiometer retains full sensitivity to any source placed close to the end loop provided its field diminishes sufficiently with distance so that it does not couple with the upper loop.

The right-hand example in the figure provides additional advantage. This geometry is actually two gradiometers mounted with one upside down. Such a configuration is not only insensitive to spatially uniform fields but also to fields

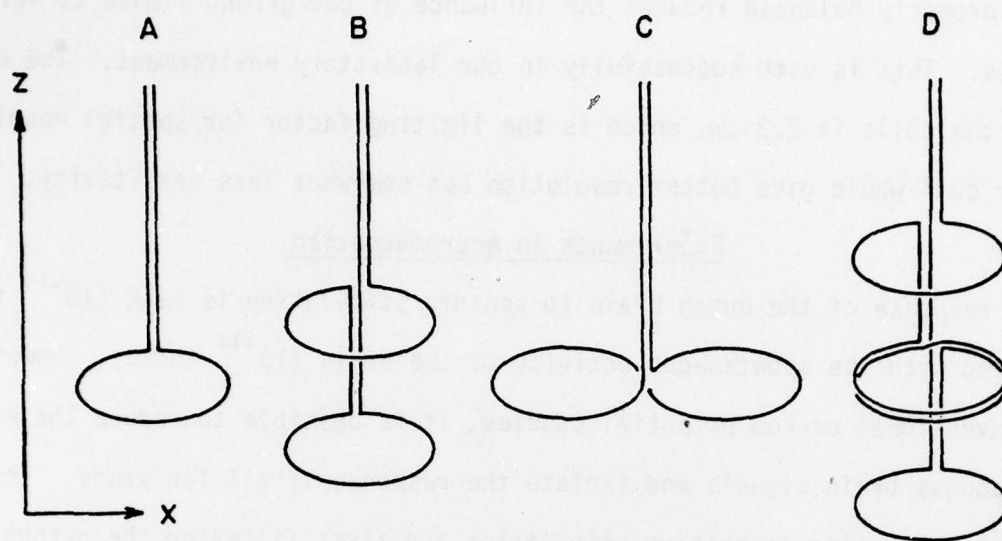


Figure 4. A few possible configurations for the detection coil of a flux transporter; A, magnetometer; B, gradiometer; C, off-diagonal gradiometer; and D, second derivative gradiometer. The plane of each loop is perpendicular to the z-axis.

with spatially uniform gradients. It is called a second derivative gradiometer and when properly balanced reduces the influence of background fields to very low levels. This is used successfully in our laboratory environment. The diameter of the coils is 2.2 cm, which is the limiting factor for spatial resolution. A smaller coil would give better resolution but somewhat less sensitivity.

Experiments in Neuromagnetism

The response of the human brain to sensory stimulation is weak (10^{-13} tesla) as compared with the spontaneous activity of the brain (10^{-12} tesla). However, as in conventional evoked potential studies, it is possible to reduce the effects of spontaneous brain signals and isolate the response itself for study. This is accomplished by using repetitive stimulation and first filtering the output of the SQUID electronics to pass only signals which are in synchronism with the stimulus and then applying the result to an averaging computer. The averaging computer stores the filtered output of the SQUID after the presentation of a single stimulus. This stored data is added to that resulting from a second presentation of the stimulus, and so on. The spontaneous activity of the brain, as well as external "noise" that is not suppressed by the gradiometer and filter, have no consistent relationship to the stimulus. Thus, the unwanted activity tends to be self-cancelling. The cumulative average of many stimulus presentations represents the response of the brain with the relatively attenuated residual noise contributing very little variability to the outcome of an experiment.

Figure 5 illustrates this averaging process as carried out in a visual experiment to be described in more detail later. The stimulus is a pattern presented at a rate of 13 Hz on an oscilloscope. Thus, the stimulus period is $1/13 = 77$ ms, as indicated on the upper horizontal axis. Equivalently, instead of dividing the period into temporal segments we could instead assign phases with a total span of 180 deg or 2π radians across one period, as shown on the lower horizontal axis. The sinusoidal curves represent the averaged responses over

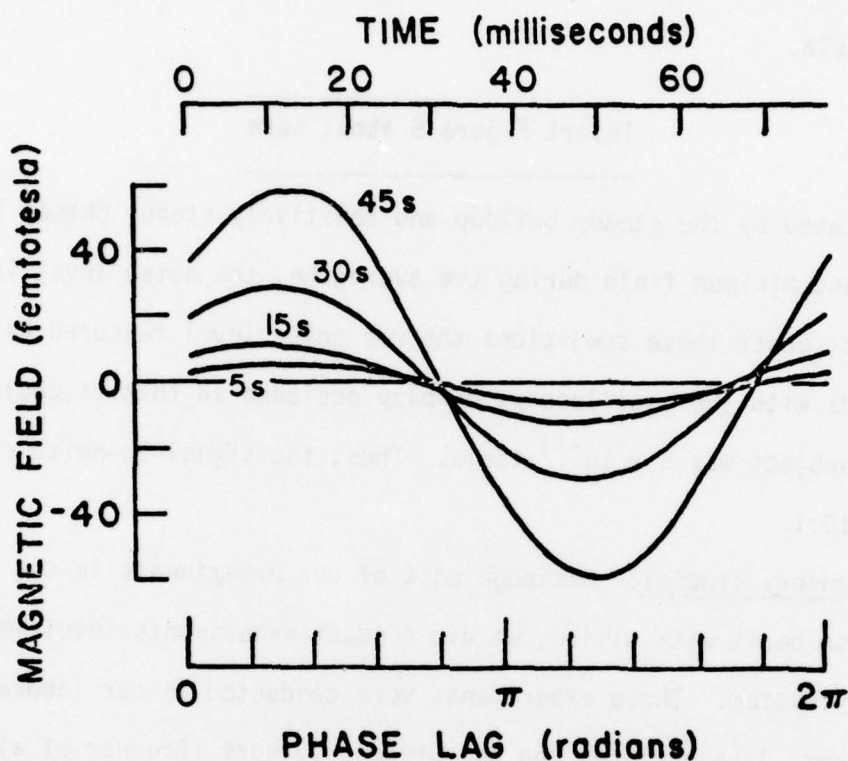


Figure 5. Cumulative average magnetic field detected near the scalp during the 77 millisecond period between two visual stimuli. The buildup of the neuro-magnetic signal after 5, 15, 30, and 45 seconds of averaging is shown. This drawing was traced from photographs taken of an oscilloscope presentation:

cumulative averaging times of 5, 15, 30, and 45 seconds. In the present instance the amplitude of the response after 45 seconds represents a field strength of 60×10^{-15} tesla.

Insert Figure 5 about here

As indicated by the steady buildup and relatively steady phases for the maximum and minimum field during the averaging, the noise level is quite low. In fact, under these conditions the rms noise level measured by averaging for 45 seconds with the oscilloscope display occluded so that it could not be seen by the subject was 5×10^{-15} tesla. Thus, the signal-to-noise ratio was better than 10:1.

Somatosensory studies: Although most of our experiments in the field of neuromagnetism dealt with vision, we did conduct experiments involving the somatosensory system. These experiments were conducted in our laboratory by Douglas Brenner, Joseph Lipton and the present authors (Brenner et al., 1978). We present them now because they provide a graphic means for describing neuromagnetic responses in general.

A very weak periodic electric current was applied transcutaneously to the little finger of one hand. This resulted in the appearance of an average neuromagnetic response on the contralateral side of the head over the posterior bank of the Rolandic fissure. This area is known to be the primary receiving area for sensory signal of somatic origin. The field pattern produced by this stimulus is illustrated in Figure 6. A similar experiment was conducted by stimulating the thumb rather than the little finger. The resulting field pattern resembled that produced by stimulation of the little finger but it was

Insert Figure 6 about here

shifted 2 cm downward toward the ear. This displacement is probably related

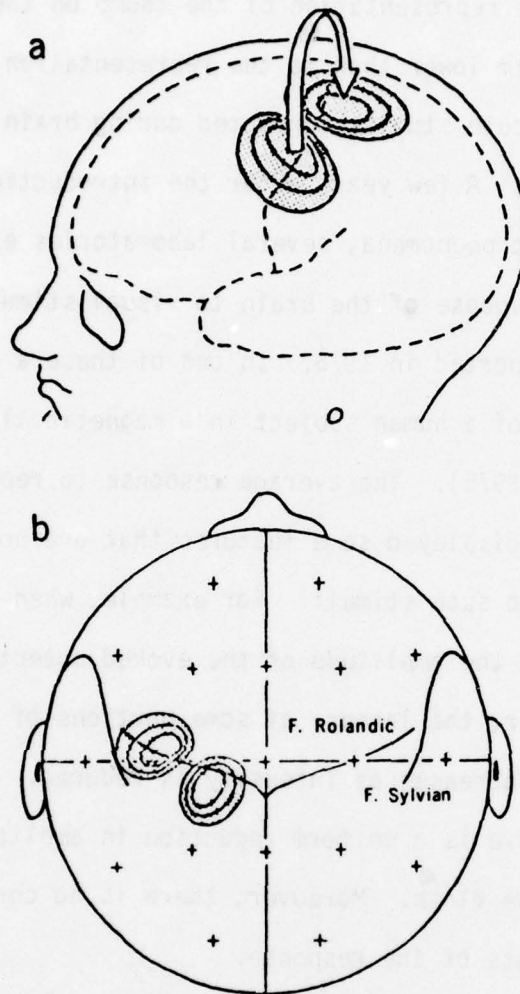


Figure 6. (a) Pattern on the left hemisphere of the normal component of the neuromagnetic field evoked by an electrical stimulation applied to the little finger of the right hand. Contours represent isochamps, or locations of equal field intensity, that are 0.9, 0.7, and 0.5 of the peak amplitude. (b) The same pattern drawn on the conventional 10-20 electrode map.

to the fact that the representation of the thumb on the somatic sensory cortex is in fact about 2 cm lower than is the representation of the little finger, as established by acute studies conducted during brain surgery.

Visual studies: A few years after the introduction of the SQUID to the study of biomagnetic phenomena, several laboratories explored the possibility of detecting the response of the brain to visual stimulation. Two successful experiments were reported in 1975. In one of these a strobe lamp was used to stimulate the eyes of a human subject in a magnetically shielded room (Tyler, Cuffin, and Cohen, 1975). The average response to repeated presentations of the flash of light displayed some features that are not displayed by classic evoked potentials to such stimuli. For example, when the intensity of the light is attenuated the amplitude of the evoked potential does not decrease uniformly. Moreover, the latency of some portions of the wave representing such evoked potentials increases as intensity is reduced. In the evoked magnetic field, however, there is a uniform reduction in amplitude with reduction in the intensity of the flash. Moreover, there is no corresponding variation in latency of components of the response.

The response described above is known as a transient response. The reason for this appellation is that sufficient time is provided between successive presentations of the flash to allow the brain to recover from one stimulus before it responds to the next. In contrast with this it is possible to present stimuli periodically at a sufficiently high frequency so that the effect of one stimulus does not wear off before the presentation of the next. In this situation the brain settles down into a steady periodic response at the frequency of the stimulus and, possibly, at one or more of its higher harmonics. This is known as the steady state response. The first detection of the steady state evoked magnetic field was also reported in 1975. This experiment was done without shielding in a normal laboratory environment (Brenner, Williamson,

and Kaufman, 1975).

In this experiment we displayed a pattern composed of luminous bars repeatedly flashed on and off on a dark screen. The tail section of the dewar, which contains the detection coil, was positioned at various places over the scalp. A well-defined signal related to the stimulus was observed only when the coil was over a relatively small area at the back of the head, near the visual cortex. It was possible to detect responses to bars flashing at frequencies from 8 Hz to 20 Hz. As our research progressed we obtained a more sensitive SQUID system which has permitted us to extend this range from 2 Hz to 40 Hz. Nevertheless the evoked magnetic field that we could detect remained confined to the region near the visual cortex. Measurements on the midline revealed no observable field higher than 11 cm above the inion (a protubance at the back of the head where the neck muscles insert into the skull). This relatively sharp localizability is consistent with the notion that the magnetic field is caused by electrical currents flowing within the cortex. Potential measurements show a much more diffuse response, with strong signals being observed even as high as the vertex at the top of the head.

These early results led us to work more intensively in the study of the visual system. The experiments to be described below were conducted with the collaboration of Douglas Brenner and with the assistance of Edward MacIin. The first of these experiments was designed to test the hypothesis that there would be a systematic variation in the steady state response as we varied the properties of the visual stimulus.

The stimulus we employed was a grating pattern composed of a sinusoidal variation of luminance across the screen of an oscilloscopic display, as illustrated in Figure 7.

Insert Figure 7 about here

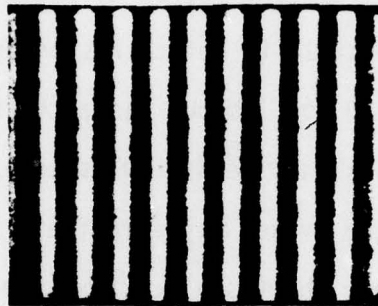


Figure 7. Grating pattern used as a visual stimulus, with the luminance varying sinusoidally across the display.

A spatial sinusoidal grating may vary in spatial frequency (the number of cycles of change in luminance per degree of visual angle), in average luminance, and in contrast. Contrast is defined as the difference between the peak and trough luminances divided by their sum. The grating is a spatial analogue to the acoustical sinusoid used to describe sounds. It is well known that any complex sound may be decomposed into a set of simple sinusoids of various amplitudes - a process known as Fourier analysis. Moreover, the auditory system is capable of performing a crude kind of Fourier analysis since it is often possible to hear the pure tones (sinusoids) making up a complex sound. This same procedure is possible when dealing with visual patterns. Any visual pattern can be decomposed into a set of sinusoidal gratings of various spatial frequencies, contrasts, average luminances and orientations. Campbell and Robson (1968) advanced the fascinating idea that the visual system may decompose complex scenes into its sinusoidal components. It is believed today that the receptive fields of single units of the visual cortex are capable of acting as spatial filters and performing this analysis.

A direct consequence of this idea was the application to spatial vision of the basic notion that a great deal of information can be transmitted along a very limited number of pathways in the visual system. This is typified by color vision. We know that it is possible to discriminate among approximately 150 different spectral hues of equal intervals in wavelength. This is possible even though there are only three types of cones in the normal human eye. Each type of cone contains a pigment with a particular absorption spectrum. Consequently, short wavelength light is more likely to excite one type of cone, intermediate wavelength light another type of cone and long wavelength light the third type of cone. The balance of neural activity in the three channels fed by the three types of cones is sufficient to define all of the perceptible hues. Is there a similar economy in spatial perception?

In the domain of spatial perception we might imagine a small number of

channels where each channel is tuned to respond to a relatively narrow band of spatial frequencies. The balance of activity among these channels might well define more complex spatial patterns.

Evidence of several types exists for this multiple channels model. Perhaps the strongest evidence is contained in the work of Graham and Nachmias (1971). The reader is simply referred to their work since this is not the place to review its details. It is sufficient to point out that the existence of this evidence for tuned spatial frequency channels makes the sinusoidal grating a useful stimulus for the study of visual processes.

We employed a standard technique for presenting grating stimuli. In this technique the vertical grating is periodically shifted horizontally by one half of a spatial wavelength. Thus, a bright bar is abruptly replaced by a dark bar and vice versa. This produces a change in the pattern without altering the adaptation level of the eye, as would occur if the display were simply turned on and off as in our first experiments. This stimulus is referred to as a contrast reversal grating. The contrast reversal gratings had 60% contrast and were presented at many different reversal rates.

The response to such stimuli is characterized by its amplitude and its phase. We shall discuss variations in response amplitude later. For the present our main concern will be with the phase of the response. The phase of the response is defined as the phase angle between the peak field directed outward from the head and the time of the reversal of contrast of the grating.

The reason for using many different reversal rates is that it is possible to compute the latency of the brain's response to periodic stimuli provided that the phase of the response is proportional to the reversal rate (temporal frequency of stimulation). Data obtained using stimuli of several different spatial frequencies are shown in Figure 8. It is obvious that for a grating of a particular spatial frequency the phase of the response is proportional

to the temporal frequency of presentation. The latencies of the responses to each of the spatial frequencies are proportional to the slopes of the lines in the figure. Thus, the latencies with which the visual system responds to gratings depends upon spatial frequency.

Insert Figure 8 about here

Since it is possible to compute latency from the slope of the phase trend, a large number of stimuli of different spatial frequencies were presented to a subject (Williamson, Kaufman, and Brenner, 1978) and the latencies of the responses were computed. A plot showing how latency of the neuromagnetic response varies with spatial frequency is shown in Figure 9. It is evident that low spatial frequencies produce short latency responses while higher spatial frequencies produce long latency responses.

Insert Figure 9 about here

In an independent experiment, Breitmeyer (1975) measured simple reaction time (RT) to gratings very similar to ours. He found that RT increased with spatial frequency. By adding a constant of 115 ms to our latency data, it was possible to obtain a very precise correlation between Breitmeyer's RT data and our latency data. The solid lines in Figure 9 are Breitmeyer's original RT data. Our own RT measurements were in good agreement with Breitmeyer's. It must be concluded that all of the variation in RT with spatial frequency is due to variation in the response of the visual system while the motor system simply adds a constant to the overall RT.

Similar measurements of neuromagnetic latencies in our somatosensory stimulation of the little finger yielded an average value of 70 ms for four subjects. A simple reaction time task was also performed. A weak stimulus

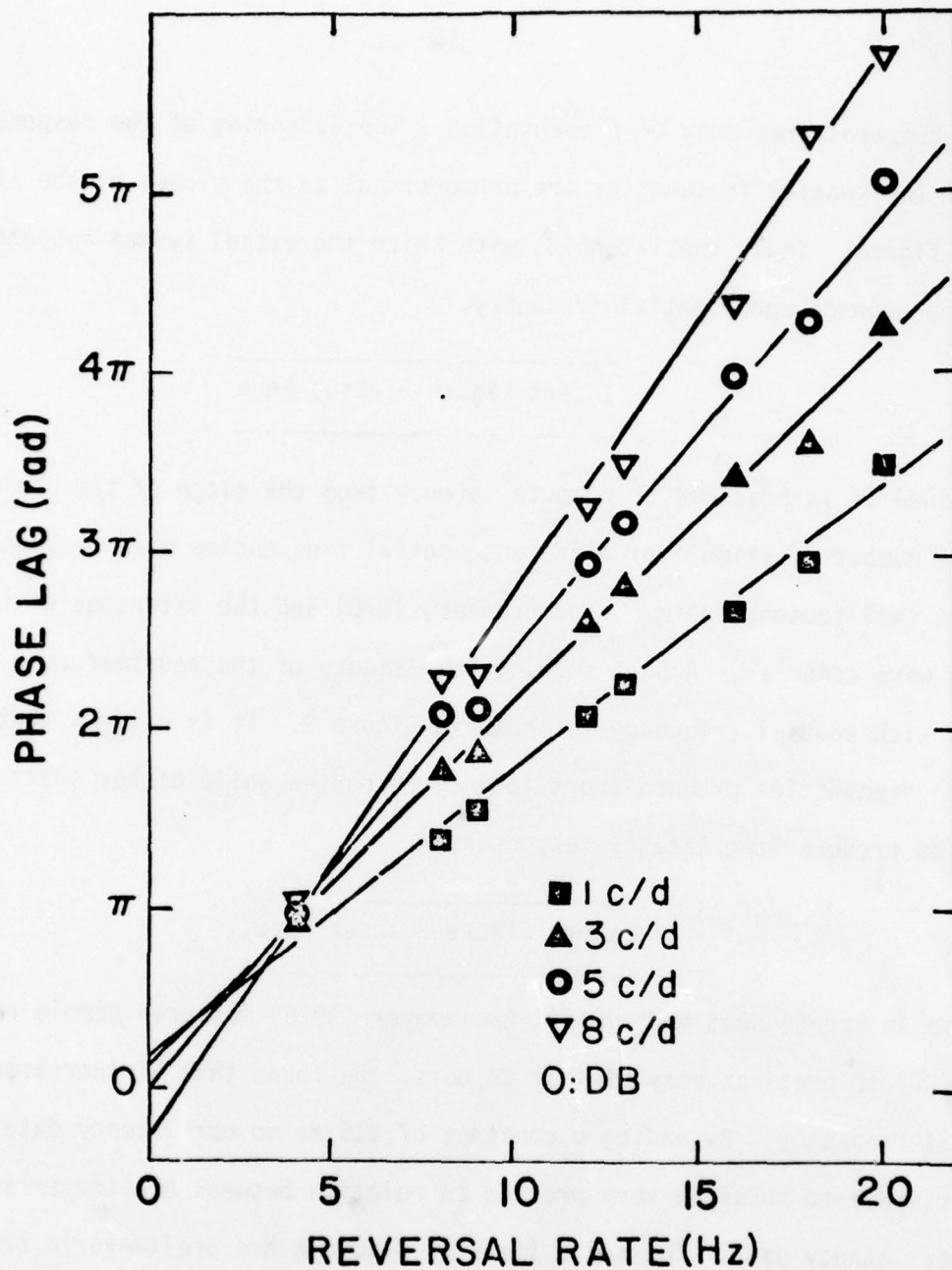


Figure 8. Phase lag of the evoked neuromagnetic response at various reversal rates of contrast of a grating pattern. Results for gratings of 1, 3, 5, and 8 cycles per degree are shown.

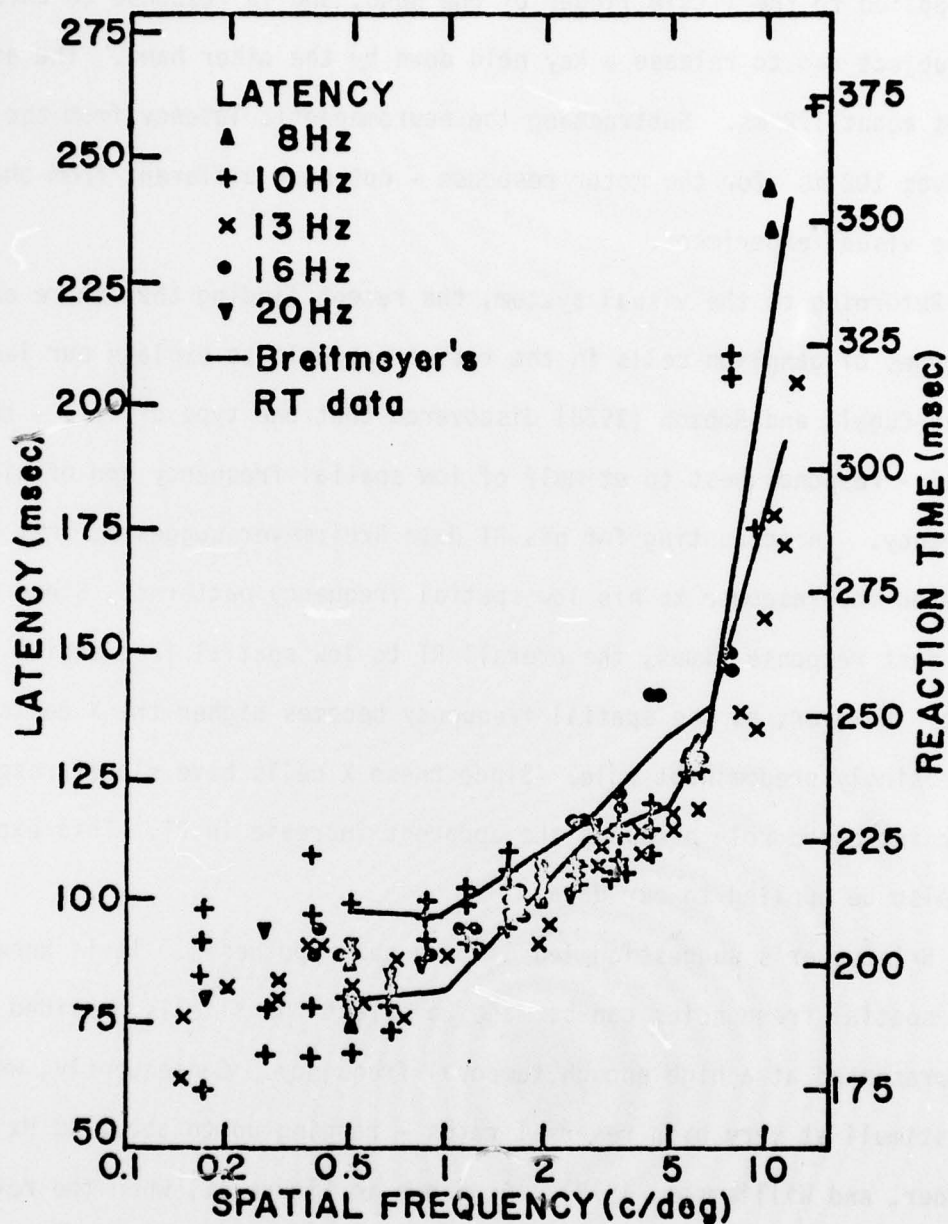


Figure 9. The data points represent the latency of the peak neuromagnetic field as obtained at 5 different contrast reversal rates. The observed independence from reversal rate is an alternative way of demonstrating the linearity of phase trends displayed in Figure 8. The lines in the graph are based upon reaction times obtained from two subjects by B. Breitmeyer (1975).

was applied to the little finger of one hand, and in response to this stimulus the subject had to release a key held down by the other hand. The average total RT was about 172 ms. Subtracting the neuromagnetic latency from the overall RT gives 102 ms for the motor response - not much different from that obtained in the visual experiment.

Returning to the visual system, the recent finding that there are at least two types of ganglion cells in the retina may help to explain our latency results. Enroth-Cugell and Robson (1968) discovered that one type of cell - the so-called Y cell - responds best to stimuli of low spatial frequency and of high temporal frequency. In accounting for his RT data Breitmeyer suggested that the Y cells mediated the response to his low spatial frequency patterns. Since these Y cells have fast response times, the overall RT to low spatial frequencies should be short. However, as the spatial frequency becomes higher the X cells play an increasingly predominant role. Since these X cells have slower response times their increased role produces the apparent increase in RT. This explanation can also be applied to our data.

Breitmeyer's suggestion led us to a new hypothesis. It is known that high spatial frequencies can be made to affect the Y cells provided that they are presented at a high enough temporal frequency. Consequently, we presented our stimuli at very high reversal rates - ranging up to about 40 Hz (Kaufman, Brenner, and Williamson, 1978). As shown in Figure 10, when the reversal rate was higher than about 20 Hz, all of the stimuli produce responses falling on a common slope. All of the phase versus frequency plots are approximately parallel to the plot obtained with a 1 cycle/deg stimulus. This implies that at high temporal frequencies all of the stimuli produce responses with the same short latency as that obtained with low spatial frequency stimuli.

Insert Figure 10 about here

Although the foregoing results are consistent with Breitmeyer's suggestion, we are still testing its validity. For example, all of our results may simply

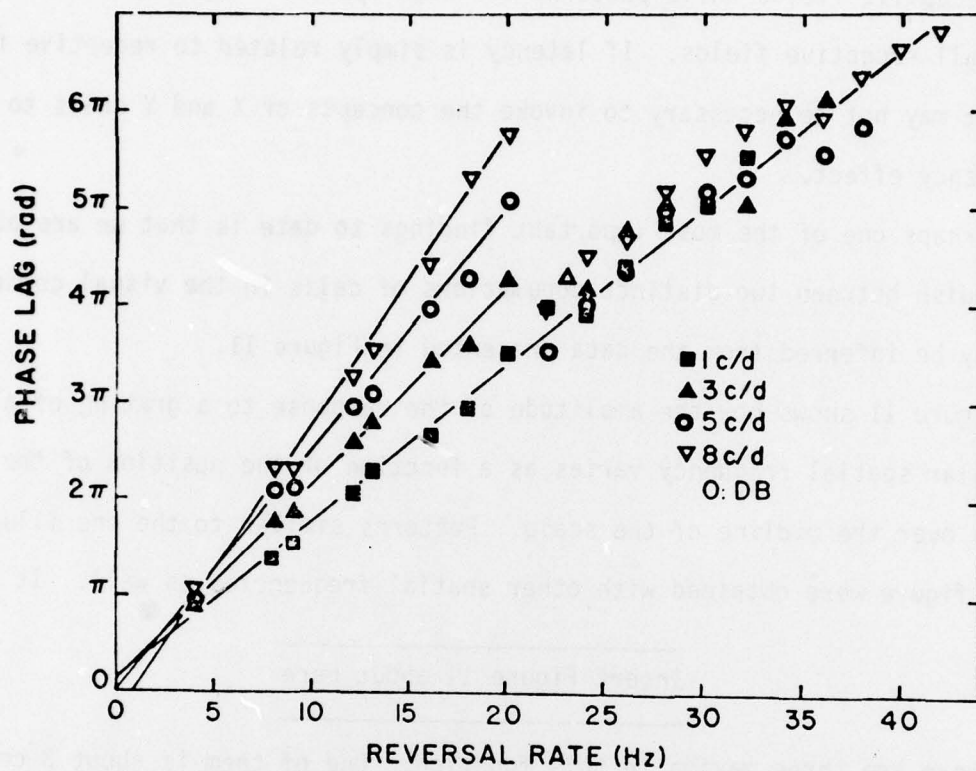


Figure 10. Pattern dependence of the phase trends obtained at low reversal rates is lost at high rates.

be due to the fact that the patterns of low spatial frequency excite cells with large receptive fields while patterns of high spatial frequency excite cells with small receptive fields. If latency is simply related to receptive field size, it may not be necessary to invoke the concepts of X and Y cells to explain the latency effect.

Perhaps one of the most important findings to date is that we are able to distinguish between two distinct populations of cells in the visual cortex. This may be inferred from the data presented in Figure 11.

Figure 11 shows how the amplitude of the response to a grating of a particular spatial frequency varies as a function of the position of the detection coil over the midline of the scalp. Patterns similar to the one illustrated in the figure were obtained with other spatial frequencies as well. It appears

Insert Figure 11 about here

that there are three maxima in this function. One of them is about 3 cm below the inion, another 5 cm above the inion and the third is about 9 cm above the inion. Also shown in Figure 11 is the variation in phase with the position of the pick up coil.

It is possible to associate the maxima of the amplitude plot with two distinct regions of activity in the brain. Phase trends relating temporal frequency to response phase were employed to ascertain the latencies with which the three regions respond to grating stimuli. The two lower regions respond with the same latency. Moreover, as indicated in the figure, the phase difference between responses in these two lower regions is nearly π . It is reasonable to infer from this that the responses at the two lower regions are produced by a common underlying source on each side of the head just above the inion. Magnetic field emerges from the scalp just above the inion and returns

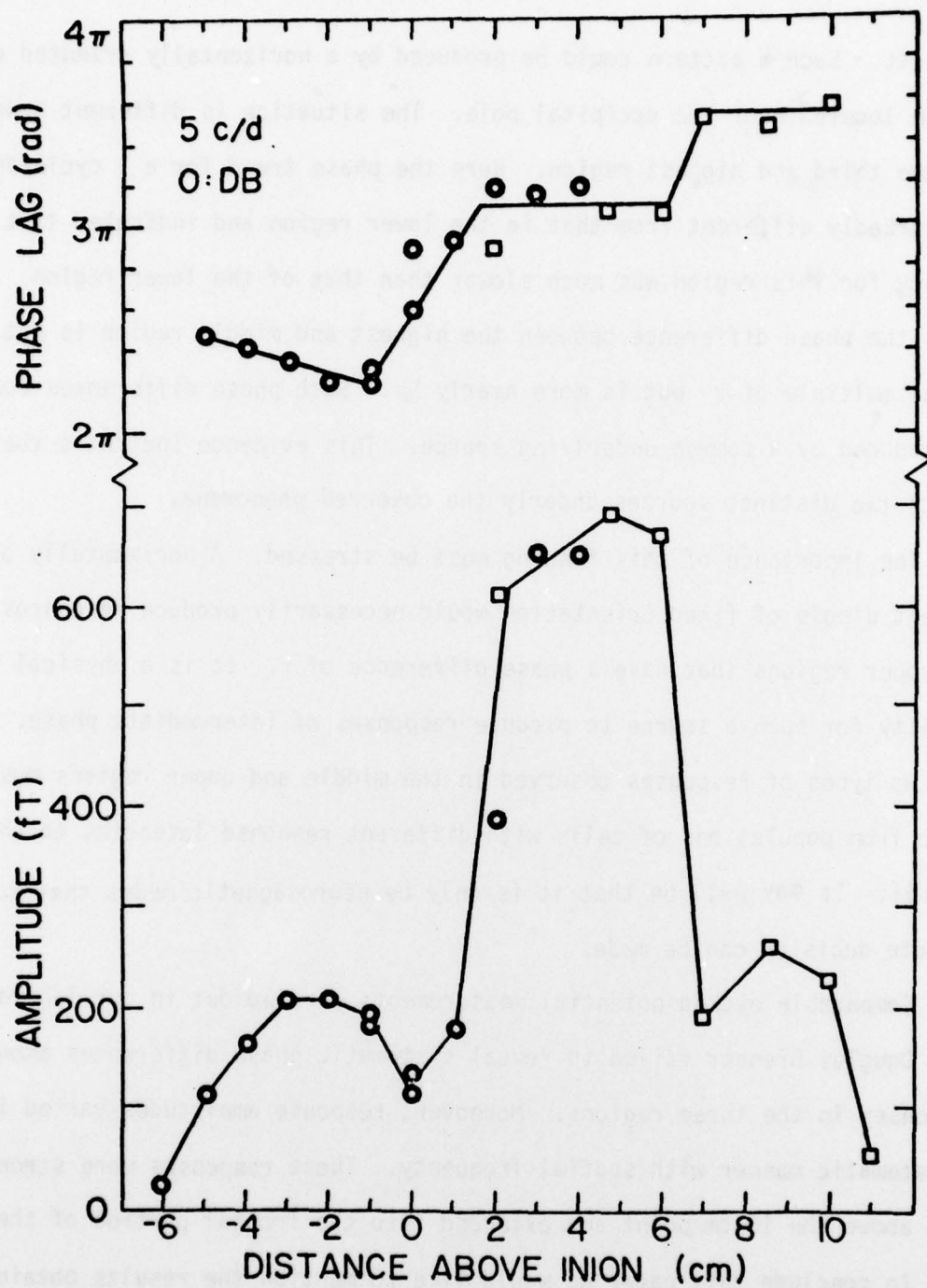


Figure 11. Variation of the phase and amplitude of the visually evoked neuro-magnetic response with position along the midline.

below it. Such a pattern could be produced by a horizontally oriented current dipole located near the occipital pole. The situation is different however for the third and highest region. Here the phase trend for a 1 cycle/deg grating was markedly different from that in the lower region and indicated that the latency for this region was much slower than that of the lower region. Moreover, the phase difference between the highest and middle region is not an integral multiple of π but is more nearly $\frac{1}{2}\pi$. Such phase differences could not be produced by a common underlying source. This evidence indicates that (at least) two distinct sources underly the observed phenomena.

The importance of this finding must be stressed. A horizontally oriented current dipole of fixed orientation would necessarily produce responses in the two upper regions that have a phase difference of π . It is a physical impossibility for such a source to produce responses of intermediate phase. Therefore, the two types of responses observed in the middle and upper regions must necessarily arise from populations of cells with different response latencies to the visual stimuli. It may well be that it is only by neuromagnetic means that such an absolute decision can be made.

Comparable evoked potential measurements carried out in our laboratory with Douglas Brenner failed to reveal systematic phase differences among the responses in the three regions. Moreover, response amplitudes varied in an unsystematic manner with spatial frequency. These responses were strongest well above the 10 cm point and extended into the frontal portion of the head.

To conclude this paper we would like to mention the results obtained thus far in an ongoing study being conducted by the authors and Douglas Brenner. In these experiments a grating stimulus is presented in either the left or right hemifields and the detection coil is located on the midline where it could respond to the activity of either hemisphere of the brain. Thus far five subjects were exposed to gratings with spatial frequencies at 1 cycle/deg and

5 cycles/deg. In two of the subjects we found that responses generated by gratings in one hemifield were 180 deg out of phase relative to the responses generated by gratings in the opposed hemifield. As indicated in Figure 12, these results could be accounted for if it is assumed that the responses are

Insert Figure 12 about here

associated with horizontally oriented and symmetrical equivalent current dipoles in the two hemispheres. This is consistent with the fact that we have finally discovered the true return paths of the fields. The magnetic fields of the responses from the lower region arise from the occipital portion of the skull and return below theinion to the base of the brain.

A systematic experiment was conducted in which the temporal frequency of stimulation (reversal rate) was varied for hemifield patterns. As before, it was found that the phase of the response is proportional to the temporal frequency of stimulation. Since the slopes of the phase trends for the two subjects already mentioned were the same regardless of the hemisphere being activated by the stimuli as shown in Figure 13, it must be concluded that their two hemispheres respond with the same latencies. However, this was not the case with the other three subjects.

Insert Figure 13 about here

One female subject had slightly different phase trends. The left hemisphere had a response latency that was about 30 msec faster than that of the right hemisphere. Another female subject's right hemisphere had a latency that was about 20 msec faster than that of the left hemisphere. Most startling of all was the finding in one male subject that one hemisphere's response lagged the other by 100 msec. Phase trends for this "anomalous" subject are shown in Figure 14. Clearly, this type of variation warrants further study with special attention to its possible clinical implications.

Insert Figure 14 about here

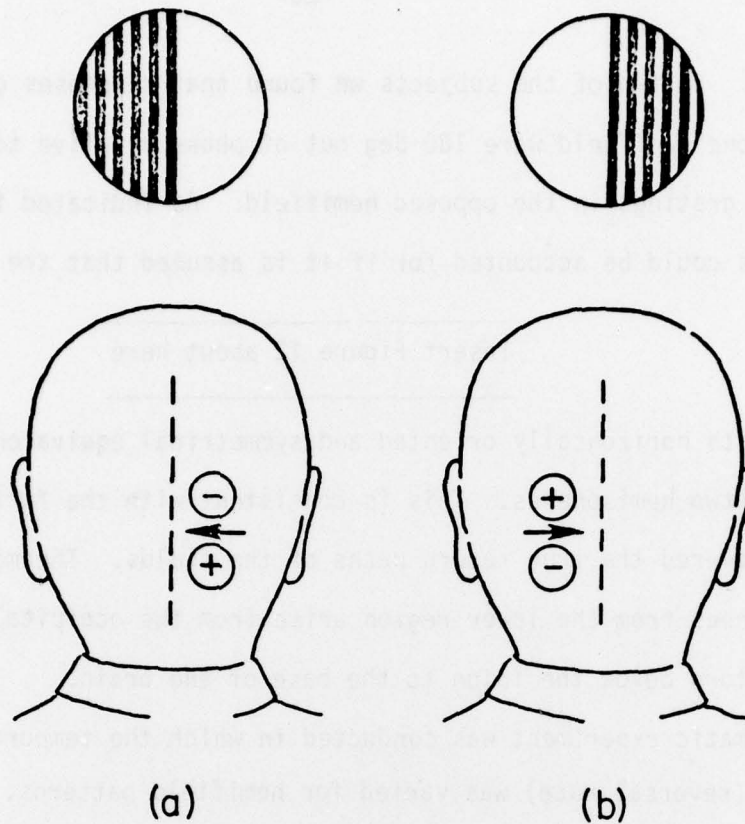


Figure 12. Visual displays illustrating at the left how a pattern in the left hemifield might evoke electrical current in the right hemisphere of the brain. The arrow schematically illustrates a horizontal current, with its accompanying magnetic field leaving the head below (+) and entering above (-). At the right is illustrated a visual stimulus in the right hemifield evoking a current in the left hemisphere, with reversed direction for its field.

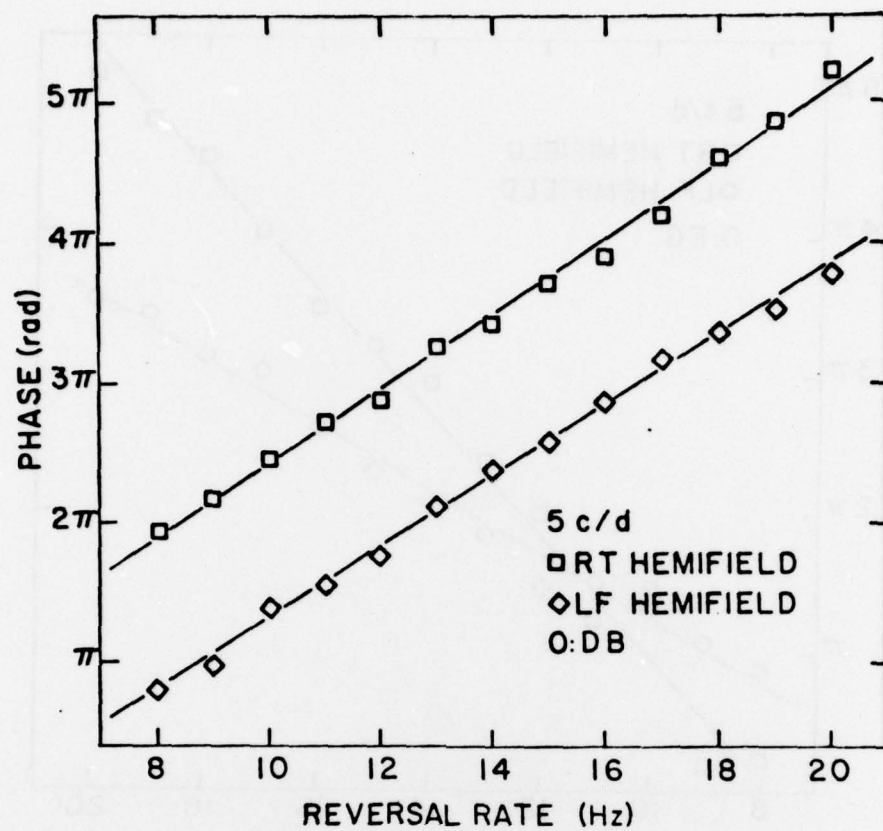


Figure 13. Phase trends for responses evoked by contrast reversal stimuli in the right hemifield and the left hemifield for a "normal" subject.

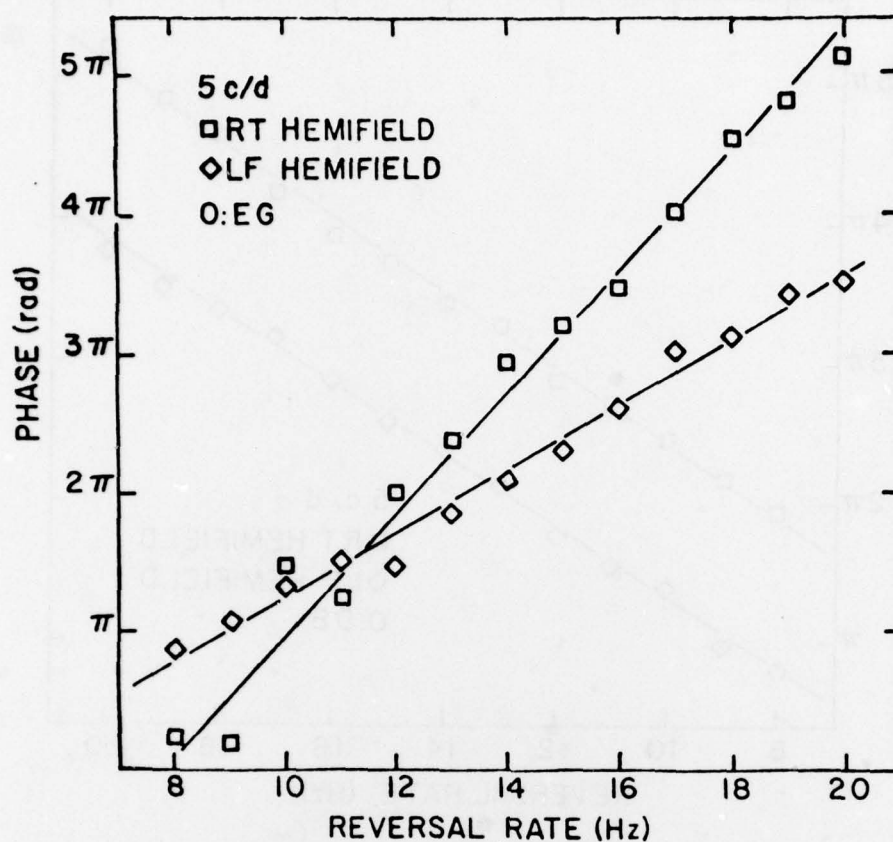


Figure 14. Phase trends for right and left hemifield stimuli from an "abnormal" subject. The latency for left hemisphere response is considerably longer than for the right hemisphere response.

It will be recalled that in most of the earlier visual studies the detection coil was located over the midline and the full visual field was stimulated, thus affecting both hemispheres. In this most recent study we found that the phase of the response to stimulation of the full visual field measured on the midline was identical in all cases to the phase of the response of one of the hemispheres. It was by moving the probe well off to one side of the midline that a phase reversal was encountered or, alternatively, by stimulating the hemiretinas separately. The seeming predominance of one hemisphere is due to the fact that when the responses of the two hemispheres are measured on the midline, one of the hemispheres produces a much stronger response than does the other. In point of fact, in most cases stimulation of one hemiretina at a time resulted in one hemisphere producing a field that was about twice as strong as is encountered when both hemiretinas are stimulated simultaneously. This could be due to the fact that when the probe is over the midline of the skull it is really farther away from one hemisphere than it is from the other. In any event, it is now clear that we can effectively double the magnitudes of our responses either by moving the probe off to one side or by stimulating one hemiretina. It is obviously necessary that experiments now be conducted in which the behavior of the hemispheres is studied separately.

Conclusion

This paper has summarized much of the work completed and in progress in the Neuromagnetism Laboratory of New York University. Based on the data obtained to date, it is clear that a new and promising method for investigating the electrical behavior of the brain is available.

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